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10/032,260

12/20/2001

Daniel Mercola

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02/18/2005

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EXAMINER

SWITZER, JULIET CAROLINE

ART UNIT

PAPER NUMBER

1634

DATE MAILED: 02/18/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| | | | |
|------------------------------|--------------------------------------|---------------------------------------|--|
| Office Action Summary | Application No. 10/032,260 | Applicant(s) MERCOLA ET AL. | |
| | Examiner Juliet C. Switzer | Art Unit 1634 | |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 23 November 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 11-27, 29 and 32-38 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 11-27, 29 and 32-38 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. This action is written in response to applicant's correspondence submitted 11/23/04. Claims 11, 20, 23, 24, and 29 have been amended, claims 1-10, 28, and 30-31 have been canceled, and claims 32-38 have been added. Claims 11-29 and 32-38 are pending. Applicant's amendments and arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections not reiterated in this action have been withdrawn. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. **This action is FINAL.**

Priority

2. This application repeats a substantial portion of prior Application No. 09/270391, filed 3/16/99, and adds and claims additional disclosure not presented in the prior application. Since this application names an inventor or inventors named in the prior application, it may constitute a continuation-in-part of the prior application. Should applicant desire to obtain the benefit of the filing date of the prior application, attention is directed to 35 U.S.C. 120 and 37 CFR 1.78. Applicant is advised that a petition is required in order to add any claim to priority in this application.

3. It is noted that in the amendment filed applicant amended the specification to include a claim to priority to application number 09/270391. However, priority is denied to this application because applicant's claim to priority is not in compliance with Rule 1.78 (see 1.78(a)(1)(ii)). No petition was filed with this amendment to the specification, and so, applicant's claim is not considered a valid claim to priority. The amendment to the specification is objected to as containing new matter in the following section of this office action. Again,

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applicant is directed to 37 CFR 1.78 and advised that a petition is required in order to add any claim to priority in this application.

Specification

4. The amendment filed 11/23/04 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: The amendment to the specification which adds the language "This application is a continuation-in-part application of patent application serial no.: 09/270,391 filed 16 March 1999 now patent no.: 6,410,233" is new matter. No basis for this amendment was provided in applicant's response.

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 112

5. Claims 20-27, 29, 33, 35 and 37-38 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

6. The amendment to claim 20 to require a step of "modulating at least one cell or at least one nucleus" appears to be new matter. The amendment to claim 33 to require "a step of modulating at least one cell or nucleus prior to cross-linking" is also new matter. All of the remaining claims are rejected because they depend from one of these two claims. The scope of the amendment includes any method of modulation prior to the cross-linking step. The

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specification, however, only discloses and discusses assays for identifying sequences regulated by a transcription factor with a pretreatment of irradiating the cells. In the remarks filed with the amendment, applicant states that claim 20 was amended to include “the limitation that the at least one cell or at least one nucleus has been stimulated with radiation,” however, this is not the amendment that was put into the claims. “Modulation” and “modulators” are discussed in the specification at page 15 as referring to the capacity to enhance or interfere with a biological activity (first paragraph), with “modulator” being referred to as a chemical such as a biological macromolecule, and thus if this definition were strictly adhered to, would exclude irradiation as a modulation. Thus, the amendment is new matter because the specification does not appear to provide support for methods which include a first step of “modulating” the cells, per se.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 20-29 are rejected under 35 U.S.C. 102(b) as being anticipated by de Belle *et al.* (BioTechniques 29: 162-169, July 2000).

This rejection is maintained because the claim to priority is not considered valid.

With regard to claim 20, de Belle *et al.* teach a method for isolating one or more genes or DNA sequences regulated by a transcription factor comprising:

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(a) cross-linking at least one transcription factor to at least one nucleic acid molecule in at least one cell or at least one nucleus, forming one or more transcription factor-nucleic acid molecule complex (p. 163, 1st column; see Figure 1);

(b) fragmenting said at least one nucleic acid molecule to form one or more transcription factor-nucleic acid molecule complex (p. 163, 2nd column); and

(c) isolating one or more nucleic acid molecule fragments from said at least one or more transcription factor-nucleic acid molecule fragment complexes to obtain at least one or more isolated nucleic acid molecule fragments (p. 163, 2nd column);

(d) hybridizing said one or more isolated nucleic acid fragments to a known complementary nucleic acid sequence in an array of sequences known to be complementary to previously identified nucleic acid molecules of known sequence (§ bridging p. 163-164); and identifying one or more genes of DNA sequences regulated by a transcription factor when said one or more genes or DNA sequences regulated by a transcription factor hybridizes to one or more isolated nucleic acid fragments on said array.

With regard to claim 21, de Belle *et al.* teach amplifying the isolated nucleic acid molecule fragments prior to identification (p. 163, 3rd column; Figure 1).

With regard to claim 22, de Belle *et al.* isolated the nucleic acid fragment from genomic DNA (p. 163).

With regard to claims 23, 24, and 25, the transcription factor is Egr-1 which is a Cys2His2 zinc finger factor.

With regard to claim 26 and 27, de Belle *et al.* use cells and the cells are living cells (p. 163, 1st column).

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With regard to claim 28, the cells are irradiated prior to cross-linking (p. 164, 2nd column).

With regard to claim 29, the cross-linking is performed using formaldehyde (Figure 1).

With regard to claim 37, the modification carried out in the modulation is irradiation of the cells which would enhance or interfere with the functional properties of at least some biological activities or properties.

With regard to claim 38, de Belle et al. teach comparing the hybridized sequences to a non-modulated (control cell that was expressing Egr, p. 163).

9. Claims 20, 21, 22, 23, 26, 27, 29 and 37 are rejected under 35 U.S.C. 102(b) as being anticipated by Orlando *et al.* (Cell, Vol. 75, 1187-1198, December 1993).

The newly added “modulating” step of claim 20 can be interpreted broadly so as to encompass any treatment of cells that effects their biological activity (for example, growing the cells in culture). This 102 rejection is applied against that broad interpretation. The specification teaches that “modulation” refers to the capacity to either enhance or interfere with a functional property of a biological activity or process (p. 15, lines 1-2) and maintaining the cells in culture meets this definition.

With regard to claim 20, Orlando *et al.* teach a method for isolating one or more genes or DNA sequences regulated by a transcription factor comprising:

(a) modulating at least one cell or at least one nucleus (p. 1195, Experimental Procedures, Cells, Labeling, and Formaldehyde Fixation; Orlando et al. are considered to be “modulating” cells when they are maintaining the cells in a medium).

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(b cross-linking at least one transcription factor to at least one nucleic acid molecule in at least one cell or at least one nucleus, forming one or more transcription factor-nucleic acid molecule complex (p. 1195, Experimental Procedures, Cells, Labeling, and Formaldehyde Fixation);

(c fragmenting said at least one nucleic acid molecule to form one or more transcription factor-nucleic acid molecule complex (p. 1196, first column); and

(d isolating one or more nucleic acid molecule fragments from said at least one or more transcription factor-nucleic acid molecule fragment complexes to obtain at least one or more isolated nucleic acid molecule fragments (p. 1196, first column);

(e hybridizing said one or more isolated nucleic acid fragments to a known complementary nucleic acid sequence in an array of sequences known to be complementary to previously identified nucleic acid molecules of known sequence (p. 1189-1190; see especially Figure 4 legend teaching that the decross-linked DNA fragment cover the transcriptional start site of the Antp-P1 promoter region); and
identifying one or more genes of DNA sequences regulated by a transcription factor when said one or more genes or DNA sequences regulated by a transcription factor hybridizes to one or more isolated nucleic acid fragments on said array (p. 1189-1190; see especially Figure 4 legend teaching that the decross-linked DNA fragment cover the transcriptional start site of the Antp-P1 promoter region).

With regard to step (d) of claim 20, Orlando *et al.* teach that the isolated fragments were hybridized to eight partially overlapping fragments of the pATP 1.0 clone that covers the Antp-P1 start site. Thus, Orlando *et al.* teach hybridizing the fragments to a known complementary

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sequence in an array of sequences and identifying the sequences regulated by Pc when hybridization occurs.

With regard to claim 21, Orlando *et al.* teach amplifying the isolated nucleic acid molecule fragments prior to identification (p. 1189 and 1196).

With regard to claim 22, Orlando *et al.* isolated the nucleic acid fragment from genomic DNA (p. 1195).

With regard to claim 26 and 27, Orlando *et al.* use cells and the cells are living cells (p. 11195).

With regard to claim 29, the cross-linking is performed using formaldehyde (p. 1195).

With regard to claim 37, the modulation step is a modification of many cells and nuclei which were maintained in the culture (p. 1195).

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

11. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

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invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 20, 21, 22, 23, 24, 25, 26, 27, 29, 37, and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Orlando *et al.* in view of Hallahan *et al.* (The Journal of Biological Chemistry, Vol. 270, No. 51, p. 30303-30309).

This rejection is applied against claim 20, 21, 22, 23, 26, 27, 29 and 37 in view of an embodiment of the claim wherein the “modulating” step is a step of irradiating the cells. This interpretation is based upon applicant’s remark that claim 20 has been amended to include the limitation that the at least one cell or at least one nucleus has been stimulated by radiation. The remarks appear to be in error since the claim was not so amended, but such a limitation is addressed in this rejection nonetheless.

Orlando *et al.* teach a method for isolating one or more genes or DNA sequences regulated by a transcription factor comprising:

(a) cross-linking at least one transcription factor to at least one nucleic acid molecule in at least one cell or at least one nucleus, forming one or more transcription factor-nucleic acid molecule complex (p. 1195, Experimental Procedures, Cells, Labeling, and Formaldehyde Fixation);

(b) fragmenting said at least one nucleic acid molecule to form one or more transcription factor-nucleic acid molecule complex (p. 1196, first column); and

(c) isolating one or more nucleic acid molecule fragments from said at least one or more transcription factor-nucleic acid molecule fragment complexes to obtain at least one or more isolated nucleic acid molecule fragments (p. 1196, first column);

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(d) hybridizing said one or more isolated nucleic acid fragments to a known complementary nucleic acid sequence in an array of sequences known to be complementary to previously identified nucleic acid molecules of known sequence (p. 1189-1190; see especially Figure 4 legend teaching that the decross-linked DNA fragment cover the transcriptional start site of the Antp-P1 promoter region); and identifying one or more genes of DNA sequences regulated by a transcription factor when said one or more genes or DNA sequences regulated by a transcription factor hybridizes to one or more isolated nucleic acid fragments on said array (p. 1189-1190; see especially Figure 4 legend teaching that the decross-linked DNA fragment cover the transcriptional start site of the Antp-P1 promoter region).

With regard to step (d) of claims 24, 25, and 28, Orlando *et al.* teach that the isolated fragments were hybridized to eight partially overlapping fragments of the pATP 1.0 clone that covers the Antp-P1 start site. Thus, Orlando *et al.* teach hybridizing the fragments to a known complementary sequence in an array of sequences and identifying the sequences regulated by Pc when hybridization occurs.

With regard to claim 21, Orlando *et al.* teach amplifying the isolated nucleic acid molecule fragments prior to identification (p. 1189 and 1196).

With regard to claim 22, Orlando *et al.* isolated the nucleic acid fragment from genomic DNA (p. 1195).

With regard to claim 26 and 27, Orlando *et al.* use cells and the cells are living cells (p. 1195).

With regard to claim 29, the cross-linking is performed using formaldehyde (p. 1195).

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Orlando *et al.* do not teach a step of modulating the at least one cell or at least one nucleus wherein the modulation comprises stimulating at least one cell or nucleus with radiation.

With regard to claims 24 and 25 Orlando *et al.* further do not teach methods in which the transcription factor is Egr-1.

Further, Orlando *et al.* teach that the method will be generally applicable to the study of other binding proteins, that the cross-link allows very stringent washing conditions which results in dramatically improved signal to noise ratios, and that the method “should open the way to the identification of in vivo target genes of low abundance transcription factors (p. 1194, ¶ bridging columns).

Orlando *et al.* do not exemplify the method in use with additional transcription factors.

Hallahan *et al.* teach that the Erg-1 is a transcription factor that is implicated in the response of cells to a variety of stressful stimuli, and that the exposure of mammalian cells to ionizing radiation results in the induction of the transcription factor Egr-1 (p. 30303).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the methods taught by Orlando *et al.* so as to have applied the method for the identification of in vivo target genes of the transcription factor Egr-1. One would have been motivated to make such a modification by the teachings of Orlando *et al.* who teach that their method can be applied for this precise purpose, and by the teachings of Hallahan *et al.* that Erg-1 is a known transcription factor. Further, in such a method one would have been motivated by the teachings of Hallahan *et al.* to have included a step of treating the cells with ionizing radiation prior to cross-linking in order to have induced production of the Erg-1 transcription factor for study, and with regard to claim 38 to have compared cells which were

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irradiated with cells that were not irradiated in order to have included a control within the assay.

Thus, in view of the teachings of the prior art, the claimed invention is prima facie obvious.

Double Patenting

13. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

14. Claims 11-27, 29, and 32-38 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-9 of U.S. Patent No. 6410233 (herein referred to as the '233 patent). Although the conflicting claims are not identical, they are not patentably distinct from each other because the methods taught in the '233 patent claims are a species of the claimed invention or recite all of the limitations of the instantly claimed invention and therefore anticipate or render obvious the claimed invention. Further, with regard to claim 20, for example, the claims of the '233 patent do not teach a single method which has (a) modulating at least one cell or at least on nucleus. However, the claims of the '233 patent include both of this steps (see claims 8 therein). It would have been prima facie obvious to have practice both of these method steps in a single invention since they are both claimed embodiments of the '233 patent and therefore on their face considered desirable steps in view of

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the claims in the '233 patent. Therefore, the practice of the methods of claims 1-9 of the '233 patent anticipates or makes obvious the practice of instant claims 11-27, 29, and 32-38.

Claim Rejections - 35 USC § 112

15. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

16. Claims 36 and 38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

17. Claim 36 recites the limitation "said hybridized array of sequences" in line two of the claim. There is insufficient antecedent basis for this limitation in the claim.

18. Further, claims 36 and 38 are confusing because it is not clear what is being compared. The claims are very cumbersome and confusing due to the use of prepositional phrases one after another but without clarity as to what is being modified. Fore example, it is not clear what the phrase "of said modulated at least one cell or at least one nucleus" modifies- the hybridized array or the known sequences.

Claim Objections

19. The previously set forth objections to the claims are moot in view of either the cancellation or amendment of the appropriate claim.

Response to Remarks

Applicant's remarks have been considered but are not persuasive.

Applicant argues that the de Belle et al. reference is not available as prior art because applicant has amended the specification to add a claim to priority. This is not persuasive because

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the priority claim is not valid, as discussed in this office action. Applicant further points out that some authors of the paper are also inventors of this application, which is irrelevant given the availability of the reference as 102(b) art. Thus, the rejection is maintained and applied to newly added claims.

Applicant argues that any potential 102(b) rejection under Orlando et al. is overcome by amendment to the claim including the limitation “that the at least one cell or at least one nucleus has been stimulated with radiation (see remarks p. 9, first full paragraph).” This is not persuasive because the claims were not so amended, as discussed in the art rejections. Thus, the rejection is maintained and applied to newly added claims.

Applicant provides five reasons why the rejection under 103 should be withdrawn. These are addressed in turn.

First, applicant points out that Orlando et al. are identifying repressed domains of known genes and Hallahan is looking for the effect of ionizing radiation on DNA synthesis and cell survival, and applicants are doing neither. This is irrelevant, as the claim excludes neither, and in fact encompasses all methods for identifying any genes or DNA sequences regulated by a transcription factor.

Second, applicant points out that they are looking at activated domains and not repressed domains. This also is not persuasive. Again, the claims do not address looking for activated or repressed domains in particular. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., the type of domain being screened for) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification

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are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Even if the recitation were in the claim, however, Orlando et al. specifically suggest that their cross-linking method has wide application in looking for genes regulated by transcription factors, teaching that the method will be generally applicable to the study of other binding proteins, that the cross-link allows very stringent washing conditions which results in dramatically improved signal to noise ratios, and that the method “should open the way to the identification of in vivo target genes of low abundance transcription factors (p. 1194, ¶ bridging columns).” Hallahan et al. specifically provide such an alternative transcription factor.

Third, applicant points out that they are looking for information on human application. Again, this limitation is not in the claims. Further, Hallahan et al. teach the study of human Egr-1, and so the totality of the rejection embraces studying human transcription factors. Applicant further argues that insect cell lines would provide no meaningful application for human cell lines, however this is purely attorney argument not supported by evidence on the record. In the instant case, the two references are both concerned with the study of transcription factors, and as noted, Orlando et al. specifically suggests applying their method to study transcription factors in general.

Fourth, applicant argues that one would not modify the teachings of Orlando et al. because one would recognize that EGR-1 would not bind to tightly wound chromatin or provide any meaningful data on identification of in vivo target genes of the transcription factor EGR-1. With regard to the fact that EGR-1 would not bind chromatin, one would certainly recognize this, as applicant points out, and using the teachings of the prior art, after cross-linking one would isolate the appropriate type of target DNA for binding of EGR-1 if one were attempting to

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study the binding of EGR-1 (for example Hallahan et al. discuss binding of EGR-1 to particular promoters). Applicant's analysis considers only the teaching of Orlando et al. in this remark, and this is a piecemeal analysis. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Finally, in a fifth point, applicant argues that ionizing radiation would not provide any useful information on mapping the polycomb-repressed domain. However, again, this is a piecemeal analysis that does not consider the totality of the rejection. The rejection states that it would have been obvious to have used the ionizing radiation in the study of EGR-1 transcription factor, not polycomb-repressed domains. When one modified of the methods of Orlando et al. to study the EGR-1 transcription factor, as discussed in the rejection, one would have been motivated by the teachings of Hallahan *et al.* to have included a step of treating the cells with ionizing radiation prior to cross-linking in order to have induced production of the Erg-1 transcription factor for study since Hallahan et al. teach that this treatment effects the binding of Erg-1 to targets.

Thus, for these reasons, the five arguments are not persuasive and the 103 rejection is maintained and applied to the amended and added claims.

Applicant sets forth that since this application has the original priority date of the parent application, a terminal disclaimer may be moot. This is not persuasive first because the claim to priority is not valid. However, even if the priority date is valid, this is not sufficient to overcome the double patenting rejection. Applicant is referred to MPEP 802.04(VI) which discusses the

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reasons why a terminal disclaimer is necessary even in cases where the filing date or priority date of the applications is the same. The rejection is maintained and applied to the newly added claims.

Conclusion

20. Claims 11-19 and 32-35 are free of the prior art. The prior art does not teach or suggest a method in which the amplifying of step (e) is completed “using said one or more nucleic acid molecule fragments as primers to obtain one or more isolated cDNA molecules.”

21. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Switzer whose telephone number is (571) 272-0753. The examiner can normally be reached on Monday through Friday, from 9:00 AM until 4:00 PM.

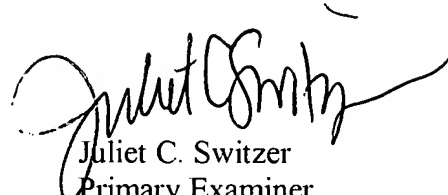
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached by calling (571) 272-0745.

The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)272-0507.

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